Docket No.: M0025.0293
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Satishchandra P. Patel

Application No.: 10/632,970 Confirmation No.: 4466

Filed: August 4, 2003 Art Unit: 1615

For: PHARMACEUTICAL COMPOSITIONS Examiner: S. T. Tran

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

As required under § 41.37(a), this brief is filed within two months of the Notice of Appeal filed in this case on October 15, 2007, and is in furtherance of said Notice of Appeal.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1205.2:

I.	Real Party In Interest
II	Related Appeals and Interferences
III.	Status of Claims
IV.	Status of Amendments

I. REAL PARTY IN INTEREST

The real party in interest for this appeal is:

Satishchandra P. Patel

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 18 claims pending in application.

B. Current Status of Claims

1. Claims canceled: 2 and 3
2. Claims withdrawn from consideration but not canceled: none
3. Claims pending: 1 and 4-20
4. Claims allowed: none
5. Claims rejected: 1 and 4-20

C. Claims On Appeal

The claims on appeal are claims 1 and 4-20.

IV. STATUS OF AMENDMENTS

All amendments filed after final rejection has been entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Cyclosporins are a class of cyclic undecapeptides with important pharmacological activities, in particular immunosuppressive, anti-inflammatory and/or anti-parasitic activities. They are very lipophilic and hydrophobic compounds, which are sparingly soluble in water, but dissolve readily in organic solvents such as methanol, ethanol, chloroform and the like. The low solubility in water results in an extremely low bioavailability of the cyclosporins when administered orally and may lead to higher dosages being required, with the consequent possibility of undesirable side effects. Providing an effective therapeutic concentration of the drug in the body when administered orally represents a considerable challenge.

Prior art oral administration formulations have often involved combinations of the cyclosporin with a surfactant, an oil, and a co-surfactant. Such formulations are intended to be diluted with water prior to drinking but this is rather inconvenient and the resulting aqueous composition has an unpleasant taste. In order to alleviate these problems, liquid compositions have been formulated into soft capsule preparations but these formulations contain ethanol in order to solubilize the cyclosporin. The ethanol can permeate the gelatin shell of the capsule and is volatile at room temperature so that the composition can vary during storage, even to the point that the cyclosporin may precipitate from the composition, with adverse effects on bioavailability.

The present invention is based upon the discovery that a pharmaceutical composition suitable for oral administration in the form of a homogeneous solution which on exposure to water or gastrointestinal fluids forms an emulsion having a particle size of less than 5 microns can be formulated with a carrier medium for the cyclosporin which is a mixture of mono- and diesters of propylene glycol with fatty acids having from 8 to 10 carbon atoms where the monoester is 50 to 60 mole % of the mixture.

One showing of support for the independent claim on appeals is as follows:

1. A pharmaceutical composition suitable for oral administration in the form of a homogeneous solution which on exposure to water or gastrointestinal fluids forms an emulsion having a particle size of less than 5 microns (page 5, lines 3-5), the solution comprising (page 5, line 6): (a) a pharmaceutically effective amount of a cyclosporin (page 5, lines 7), (b) a carrier medium comprising a mixture of mono- and diesters of propylene glycol with fatty acids having from 8 to 10 carbon atoms or with mixtures of such fatty acids (page 5, lines 8-11), wherein the monoester makes up between 50 and 60 mol % of the mixture (page 5, lines 21-22), and (c) a non-ionic surfactant having a hydrophilic lipophilic balance (HLB) greater than 10 (page 5, lines 12-13).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The claims have been rejected under 35 U.S.C. § 103 over Mulye (WO 00/33862).

VII. ARGUMENT

Cyclosporins are cyclic undecapeptides with immunosuppressive, anti-inflammatory and/or anti-parasitic activities. They are characterized by being very lipophilic and hydrophobic compounds, sparingly soluble in water, but dissolving readily in organic solvents such as alcohols, chloroform and the like. Unfortunately, the low water solubility results in extremely low bioavailability of the cyclosporins when they are administered orally and this may lead to higher dosages being required, with the consequent possibility of undesirable side effects. As a result, providing an effective therapeutic concentration of the drug in the body when administered orally is challenging.

Prior art oral administration formulations have often involved combinations of the cyclosporin with a surfactant, an oil, and a co-surfactant. Such formulations are diluted with water prior to drinking but this is inconvenient and the resulting aqueous composition has an unpleasant taste. In order to alleviate the problems of having to dilute the composition with water prior to oral administration, and the unpleasant taste of the resulting solution, liquid compositions have been formulated into soft capsule preparations but these formulations contain ethanol in order to solubilize the cyclosporin. The ethanol can permeate the gelatin shell of the capsule and is volatile at room temperature so that the composition can vary during storage, even to the point that the cyclosporin may precipitate from the composition, with adverse effects on bioavailability.

Another problem in formulating cyclosporin is the formulations are quite hygroscopic. This is particularly important in the case when the delivery form is a soft gel capsule because if water is absorbed from the shell of the soft gel capsule, then the shell becomes brittle and liable to break before being ingested.

There is a continued need to provide oral administration cyclosporin formulations having high cyclosporin concentrations (thereby reducing the size of capsule required for a given dosage), which exhibit high oral bioavailability, and which are stable upon storage, particularly stable against precipitation of the cyclosporin upon storage.

The present invention is based upon the discovery that a pharmaceutical composition suitable for oral administration in the form of a homogeneous solution which on exposure to water or gastrointestinal fluids forms an emulsion having a particle size of less than 5 microns can be formulated with the cyclosporin and a surfactant if the carrier medium for the cyclosporin is a mixture of mono- and diesters of propylene glycol with fatty acids having from 8 to 10 carbon atoms in which the monoester is 50 to 60 mole % of the mixture. This result is particularly surprising and unpredictable in light of the Mulye reference (WO 00/33862) which is the basis of the rejection on appeal here.

Mulye discloses that it was discovered that the cyclosporin-surfactant formulation problem could be addressed by the use of a 6 to 18 carbon atom fatty acid ester of propylene glycol carrier system provided that the monoester constitutes at least about 60 weight percent of the esters. The monoester content employed is preferably greater than 70%, and most preferably more than 90% (page 16, lines 20-23).

Contrary to the teachings of Mulye, the present invention is based on the discovery that effective solubilization of the cyclosporin-surfactant could be obtained when a lower amount of monoester content was employed, particularly between 50 and 60 mole %, and the fatty acid contained 8 to 10 carbon atoms. The combination of the correct fatty acid and the correct monoester content allows effective solubilization of the cyclosporin. Furthermore, reducing the monoester content reduces the hygroscopicity of the

formulation. The compositions of the appealed claims exhibit excellent stability upon storage, and high concentrations of cyclosporins in the compositions are achieved.

The compositions of the present invention are not obvious over Mulye and, in fact, are directly contrary to what this reference teaches those of ordinary skill in the art. Thus, Mulye teaches the skilled person that a propylene glycol ester of a 6 to 18 carbon atom fatty acid in which the monoester is at least about 60 % by weight and the diester is no greater than 40 % by weight must be used. It demonstrates in Comparative Example 2 that when propylene glycol laurate, i.e., esters of a C_{12} fatty acid, with a monoester content of 45-50% was used, the cyclosporin failed to become solubilized, and precipitation and crystal growth occurred after two weeks.

The composition of the present invention in differs from Mulye in two respects, namely that the fatty acid has from 8 to 10 carbon atoms rather than 6 to 18, and that the monoester is less than 60 mole percent of the monoester/diester mixture. In an Advisory Action, the Examiner observed that "about" 60 wt% could encompass 58-59 %. However, this observation fails to take into account that by virtue of the presence of the second ester moiety, the diester is heavier than the monoester, and therefore, 60 mole percent will be substantially less than 60% monoester on a weight basis. A 60 mole % content of the propylene glycol monoester of the C_8 fatty acid in a mixture with propylene glycol C_8 fatty acid diester corresponds to 48 weight percent[1]; and the corresponding conversions into weight percents for the C_9 and C_{10} fatty acid monoesters are lower than for the C_8 fatty acid. Thus, Mulye requires at least "about" 60 wt% monoester (or 58% and higher according to the Examiner) while the invention uses less than 50 wt%.

[1] 60 moles of mono-C_8 ester of propylene glycol (mol. wt. = 202) weighs 12120 and 40 moles of diester (mol. wt. = 328) weighs 13120; Accordingly, weight percent = 100(12120/12120 + 13120) = 48 wt% monoester

Mulye points out, time and time again, that the monoester must be at least about 60% by weight, an amount which when translated into mole % is in excess of 70 m%. At the top of page 15, and again at page 34, lines 14-16, this percentage is stated to be "essential". Mulye's Comparative Examples 1 and 2 demonstrate that formulations with 10 wt% C_8 fatty acid monoester or 45-50 wt% C_{12} fatty acid monoester precipitated and crystallized after 1 week or 2 weeks, respectively. From this, Mulye concludes that 50 wt% monoester (of a C_{12} fatty acid) shows precipitation and crystal growth while a 60 wt% monoester formulation does not (page 35, lines 14-18). The monoester must also be at least about 60 wt% in order to realize a non-hydroscopic composition (page 25, line 30). Accordingly, Mulye teaches that the composition must contain more than about 60 wt% monoester in order to be storage stable and non-hydroscopic, and thus teaches the skilled person that a composition in which the monoester is less that about 60% by weight will not be storage stable and will be hydroscopic.

The Advisory Action seeks to ignore the difference in monoester content on the ground of optimization. However, as observed in the case of *In re Sebek*, 175 USPQ 93, 95 (C.C.P.A. 1972) that "while it may ordinarily be the case that the determination of optimum values for the parameters of a prior art process would be at least prima facie obvious, that conclusion depends upon what the prior art discloses with respect to those parameters. Where, as here, the prior art disclosure suggests the outer limits of the range of suitable values, and that the optimum resides within that range, and where there are indications elsewhere that in fact the optimum should be sought within that range, the determination of optimum values outside that range may not be obvious." In the case on appeal here, the prior art teaches the critical minimum amount of the monoester value is

60 wt% and the optimum is about 90%. Determination that an amount of less than 50% is better if the fatty acid has 8 to 10 carbon atoms is clearly unexpected and not predicable.

The Applicant surprisingly discovered that when the fatty acid was a 8 to 10 carbon atoms and also when the monoester was less than 50 weight percent rather than greater than about 60% by weight, the composition was storage stable. This result is demonstrated in the working examples and also verified and discussed in the Rule 132 Declaration.

The Declaration points out in paragraph 3 that two compositions which differed only in the monoester content gave very different results when tested under the same conditions. At 10 wt% monoester, there was crystallization and precipitation after 1 week whereas at between 50 and 60 mole percent, the solution remained clear for at least 4 weeks. It also points out that when the fatty acid carbon content was increased to 12 carbon atoms (Comparative Example 2), the solution was unstable at 4 weeks storage as indicated by being hazy. These results are, as stated, surprising, unexpected, and unpredictable.

Mulye teaches the monoester content is most preferably more than 90% (page 16, lines 20-23) and the resulting composition is "non-hydroscopic" (page 25, line 30). The Rule 132 Declaration shows in paragraph 5 that where the monoester content of a C_8 fatty acid propylene glycol ester mixture was 90 weight percent, water absorption was 3-4%, whereas when the content was a lower 50-60 mole percent, absorption was only 1-2%. Mulye tells the skilled artisan that when the monoester content is lowered, the water absorption should be higher than 3-4%, and realizing a lower absorption when lowering

the content is directly contrary to that disclosure. The reduced moisture absorption is also, as stated, surprising, unexpected, and unpredictable.

The invention of the appealed claims is both contraindicated by Mulye and also provides results which are clearly surprising, unexpected, and unpredictable. The invention is unobvious.

The rejection on appeal should be reversed.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A.

Dated: December 13, 2007

Respectfully submitted,

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APPENDIX A

Claims Involved in the Appeal of Application Serial No. 10/632,970

1. A pharmaceutical composition suitable for oral administration in the form of a homogeneous solution which on exposure to water or gastrointestinal fluids forms an emulsion having a particle size of less than 5 microns, the solution comprising: (a) a pharmaceutically effective amount of a cyclosporin, (b) a carrier medium comprising a mixture of mono- and diesters of propylene glycol with fatty acids having from 8 to 10 carbon atoms or with mixtures of such fatty acids, wherein the monoester makes up between 50 and 60 mol % of the mixture, and (c) a non-ionic surfactant having a hydrophilic lipophilic balance (HLB) greater than 10.

4. A pharmaceutical composition according to claim 1, wherein the cyclosporin is 5 to 20% by weight of the composition, the carrier medium is 35 to 60% by weight of the composition, and the non-ionic surfactant is 20 to 50% by weight of the composition.

5. A pharmaceutical composition according to claim 1, wherein the cyclosporin is 15 to 20% by weight of the composition, the carrier medium is 40 to 55% by weight of the composition, and the non-ionic surfactant is 30 to 40% by weight of the composition.

6. A pharmaceutical composition according to claim 1, wherein said carrier medium consists of a mixture of mono- and diesters of propylene glycol with capric and caprylic acids.

7. A pharmaceutical composition according to claim 1, wherein said carrier medium consists of a mixture of mono- and diesters of propylene glycol with caprylic acid.

8. A pharmaceutical composition according to claim 1, wherein the cyclosporin is 1 to 25% by weight of the composition, the carrier medium is 20 to 80% by weight of the composition, and the non-ionic surfactant is 5 to 60% by weight of the composition.

9. A pharmaceutical composition according to claim 1, wherein the non-ionic surfactant is selected from the group consisting of: polyoxyethyled products of hydrogenated vegetable oil, polyethoxylated castor oil, polyethoxylated hydrogenated castor oil, polyoxyethylene-sorbitan-fatty acid ester, polyoxyethylene castor oil derivative, and mixtures thereof.

10. A pharmaceutical composition, according to claim 9, wherein the non-ionic surfactant is selected from the group consisting of polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, PEG-30 hydrogenated castor oil, PEG-40 hydrogenated castor oil, PEG-50 hydrogenated castor oil, PEG-60 hydrogenated castor oil, polyoxyethylene 40 castor oil, polyoxyethylene 60 castor oil, polyoxyethylene 35 castor oil, and mixtures thereof.

11. A pharmaceutical composition according to claim 1, further comprising an antioxidant.

12. A pharmaceutical composition according to claim 11, wherein the antioxidant is selected from the group consisting of BHA, BHT, and alpha-tocopherol.

13. A pharmaceutical composition according to claim 1, wherein the cyclosporin is Cyclosporin A.

14. A pharmaceutical composition according to claim 1, wherein the cyclosporin is 5 to 400 mg and is 1 to 25% by weight of the composition, the carrier medium is 20 to 80% by weight of the composition and is a mixture of mono- and diesters of propylene glycol with capric and caprylic acids or a mixture of mono- and diesters of propylene glycol with capric and caprylic acids in which the monoester is between 50 and 60 mol % of the mixture of mono- and diesters, the non-ionic surfactant is 5 to 60% by weight of the composition and has a HLB greater than 12, and the composition contains antioxidant in an amount of from 0.01% to 2% by weight of the composition.

15. A pharmaceutical composition according to claim 1, wherein the cyclosporin is 20 to 200 mg of Cyclosporin A and is 15 to 20% by weight of the composition, the carrier medium is 40 to 55% by weight of the composition and is a mixture of mono- and diesters of propylene glycol with capric and caprylic acids or a mixture of mono- and diesters of propylene glycol with capric and caprylic acids in which the monoester is between 50 and 60 mol % of the mixture of mono-and diesters, the non-ionic surfactant is 30 to 40% by weight of the composition and has a HLB greater than 14, and

the composition contains antioxidant in an amount of from 0.5% to 1% by weight of the composition.

16. A pharmaceutical composition according to claim 15, formulated as a drinking solution.

17. A pharmaceutical composition according to claim 1, formulated as a drinking solution.

18. A pharmaceutical composition according to claim 1 formulated as a hard or soft capsule.

19. A pharmaceutical composition according to claim 16 contained within a soft gelatine capsule.

20. A pharmaceutical composition according to claim 1 contained within a soft gelatine capsule.

APPENDIX B

EVIDENCE PURSUANT TO 37 CFR § 1.132 OF RECORD

Docket No.: M0025.0293

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Satishchandra P. Patel

U.S. Patent Application Serial No.: 10/632,970

Filed: August 4, 2003

Title: PHARMACEUTICAL COMPOSITIONS

DECLARATION UNDER RULE 132

SATISHCHANDRA P. PATEL, declares that

1. I am the applicant in the above identified application.

2. The experimental work described in the examples of the above identified application were done by or for me and gave the results therein set forth.

3. The Mulye reference which has been cited by the Examiner relates to the use of a propylene glycol ester of a 6 to 18 carbon atom fatty acid of which at least 60% by weight based on the total weight of the propylene glycol ester is monoester. It states that a content of at least 60% monoester is essential and that the diesters do not aid in solubilizing a lipophilic drug. In Comparative Example 1, it is shown that a formulation containing 10% monoester precipitates and crystallizes after one week and in Comparative Example 2, a composition in which the monoester content is about 45 to 50 percent precipitated with crystal growth after two weeks.

4. I discovered that when the esters are of fatty acids having from 8 to 10 carbon atoms and the monoester is between 50 and 60 mol percent of the mixture of the mono- and diesters, surprising and unexpected effects were realized. These results were not predicable.

5. For instance, as shown in my Example 1, a composition containing mono- and diesters with caprylic acid in which the monoester content was between 50 and 60% provided an initial clear solution and the solution remained clear when stored for four weeks at either 25°C or 40°C.

In Mulye's Comparative Example 1, a mixture of esters of the same fatty acid in which the monoester was 10% showed crystallization and precipitation after one week at 25°C as opposed to my invention where a clear solution was maintained for at least 4 weeks at the same temperature at a monoester content between 50 and 60%. The fact that increasing the monoester content to between 50 and 60% did not result in precipitation and crystallizing is surprising, unexpected and unpredictable, particularly since the reference indicates that the monoester content must be at least 60%, and preferably much higher, in order to achieve this result. Comparative Example 2 in my application shows that similar good storage results were not achieved when a 12 carbon atom fatty acid was used as the esterifying agent and this result further shows the result when an 8 to 10 carbon atom fatty acid is used is surprising, unexpected and unpredictable.

5. Hygroscopicity tests were carried out with compositions in which the propylene glycol ester was a mixture of mono- and diesters of C_8 fatty acid. When the monoester content was about 90%, which is indicated to be the most preferred amount in the Mulye reference, the absorption of moisture from a soft gel capsule was 3-4% whereas when the monoester content was between 50 and 60%, the absorption was only 1-2% moisture. This reduced moisture absorption is also surprising, unexpected and unpredictable.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 8 August ~~May~~ 2007

Satishchandra P. Patel

APPENDIX C

No related proceedings are referenced in II. above, hence copies of decisions in related proceedings are not provided.